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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/725,214	12/01/2003	Muraleedharan G. Nair	MSU 4.1-672	4443

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EXAMINER	
FLOOD, MICHELE C	
ART UNIT	PAPER NUMBER
1655	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/10/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/725,214	NAIR ET AL.	
	Examiner	Art Unit	
	Michele Flood	1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 October 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 5-10* is/are pending in the application.

4a) Of the above claim(s) *8-10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 5-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Acknowledgment is made of the receipt and entry of the amendment filed on October 10, 2006 with the addition of newly submitted Claims 8-10. Further acknowledgment is made of the receipt and entry of the supplemental declaration of Muraleedharan G. Nair filed under 37 C.F.R. 1.132.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Election/Restrictions

Newly submitted claims 8-10 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Claims 8-10 are directed to a method for suppressing multiplicity in a mammal with a mutation in adenomatous polyposis colic (APC) which comprises providing an effective amount of a composition which consists essentially of malvidin as an active ingredient to the mammal in an amount and over a period of time sufficient to suppress the adenoma multiplicity in the mammal, whereas the originally presented invention was directed to a method for the *in vivo* inhibition in a mammal of proliferation in the stomach, colon and in both the stomach and the colon of cancer cells comprising providing an effective amount of a composition which consists essentially of malvidin as an active ingredient to the mammal so as to inhibit the proliferation of the cells. The originally presented invention did not encompass the limitation of administering an effective amount of the claim-designated ingredient to a mammal with a mutation in adenomatous polyposis coli

to provide a method of suppressing multiplicity in a mammal. Therefore, the two methods are distinct and separate. The two inventions above are independent and distinct, each from the other. The search for each of the above inventions is not co-extensive particularly with regard to the literature search. Further a reference which would anticipate the invention of one group would not necessarily anticipate or even make obvious another group. Finally, the consideration for patentability is different in each case. Thus, it would be an undue burden to examine all of the above inventions in one application.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, Claims 8-10 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claims 1 and 5-7 are under examination.

Response to Arguments

Claim Rejections - 35 USC § 112

Claim 1, as amended, and Claims 5-7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an *in vitro* method for inhibiting the proliferation of HCT-116 colon cancer cells and AGS stomach cancer cells comprising contacting the cells with an effective amount of a composition consisting essentially of malvidin, does not reasonably provide enablement for a method for *in vivo*

suppression in a mammal of multiplicity in the stomach, colon and in both the stomach and colon of any and all colon cells and/or any and all stomach cancer cells which comprises providing an effective amount of malvidin as an active ingredient to the mammal so as to inhibit the proliferation of the cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. Full consideration was given to Applicant's arguments and the statements made therein the Declaration under 37 C.F.R. § 1.132 of one the inventors of the present application, Muraleedharan G. Nair, however the rejection remains essentially same for the reasons set forth in the previous Office action and for the reasons set forth herein.

The factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands*, 858 F.2d 731, 737, 8 USPQ2D 1400, 1404 (Fed. Cir. 1988) (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the level of one of ordinary skill; (e) the level of predictability in the art; (f) the amount of direction provided by the inventor; (g) the existence of working examples; and (h) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. While all of these factors are considered, a sufficient number are discussed below so as to create a *prima facie* case.

Nature of the Invention. The claims are drawn are to a method for *in vivo* inhibition suppression in a mammal of multiplicity in the stomach, colon and in both the stomach and colon of cancer cells which comprises providing an effective amount of malvidin as an active ingredient to the mammal so as to suppress the multiplicity of the

cells. The claims are further directed to the method of claim 1 wherein the cells are in a mammal and the malvidin is feed orally to the mammal. The claims are further directed to the composition of claim 1 wherein the composition is in a pharmaceutical carrier; and wherein the stomach cell is AGS and the colon cell is HCT 156 (An apparent typographical error in line 2 of Claim 7; See "*Claim Objections*", set forth below.) both as maintained by the American Type Culture Collection.

Breadth of the Claims. The claims are broad in that the multiplicity of any and all stomach or colon cancer cells in both the stomach and colon of a mammal is suppressed comprising the administration of an effective amount of a composition which consists essentially of malvidin as an active ingredient is administered to a mammal so as to provide a method for *in vivo* suppression in a mammal of multiplicity of the aforementioned cancerous cells. The complex nature of the subject matter of the invention is clearly exacerbated by the breadth of the claims.

Guidance of the Specification and Existence of Working Examples. The specification envisions that the oral administration of a therapeutically effective amount of a composition to a mammal bearing cancerous cells in the stomach or colon, or both in the stomach and the colon will provide a method for the *in vivo* suppression in a mammal multiplicity in the stomach or the colon, or both in the stomach in the colon of cancer cells comprising the administration of an effective amount of a composition consisting essentially of malvidin as an active ingredient to the mammal so as to suppress multiplicity of the cancerous cells.

While Applicant has reasonably disclosed an *in vitro* method for inhibiting the proliferation of colon cancer (HCT-116) cells and stomach (AGS) cancer cells comprising incubating the American Type Culture Collection (Rockville, MD) human cancer cell lines in the presence of malvidin, Applicant has not demonstrated an *in vivo* method comprising orally administering an effective amount of the claim-designated composition to a mammal to provide the claimed beneficial functional effect for the suppression in a mammal of multiplicity in either the stomach or the colon, much less in both the stomach and the colon of either HCT-116 colon cancer cells or AGS stomach colon cancer cells, much less the claimed beneficial functional effect for the suppression of multiplicity in either the stomach or the colon of any and all colon cancer cells or stomach cancer cells comprising providing an effective amount of a composition consisting essentially of malvidin, and wherein the malvidin is fed orally to the mammal, as broadly claimed by Applicant. For example, at [0043] of the present application, Applicant discloses, "Malvidin and pelargonidin were in particular found to be excellent inhibitors of stomach and colon cancer cell lines *in vitro*. " However, nowhere in the present specification, as originally filed, does Applicant disclose a method comprising the oral administration of an effective amount of a composition consisting essentially of malvidin to a mammal in need thereof to suppress in a mammal multiplicity in either stomach or colon cancer cells therein the mammal or data there from. Instead, Applicant discloses only an *in vitro* method for the inhibition of the proliferation of colon (HCT) and stomach (AGS) cells comprising contacting the human cancer cell lines in the presence of dose amounts of malvidin. Given the limited data as to the cancer

model used to assess the efficacy of the disclosed composition and the limited disclosure other than the mere mention that the disclosed compositions were inhibitors of the claim-designated human stomach and colon cancer cell lines *in vitro*, it seems highly unlikely that one of skill in the art would be able to use the claim-designated composition for the *in vivo* suppression in a mammal multiplicity in either the stomach and/or colon of the claim-designated human stomach and/or colon cancer cell lines, much less any and all stomach and/or colon cancer cells, comprising providing the mammal with an effective amount of a composition consisting essentially of malvidin, even after extensive experimentation.

Predictability and State of the Art. It should also be noted that the state of the art at the time of filing of the present specification suggested that the delivery of therapeutic drugs which exhibit anti-tumor activity in cancer models do not necessarily have the same beneficial functional effect in humans as disclosed by Fredic Golden (Gorman, Christine. Cancer, "How to tell the hype from the hope: A Special Report", Time, 1998, pages 37-46.) and as disclosed by Trisha Gura ("Cancer Models: Systems for Identifying New Drugs are Often Faulty", Science, 1997, Vol. 278, pages 1041-1042.). Gura further discloses various different cancer models other than murine cancer models that are not predictive of the anti-cancer activity of potential anticancer agents when delivered to humans. In another instance, Jain (Jain, Rakesh K., "Delivery of molecular medicine to solid tumors", Science (1996), Vol. 271, pages 1079-1080.) discloses that while promising chemotherapeutic agents exhibit activity against cancer cells *in vitro* and *in vivo* tumor systems, these same agents heralded as breakthrough drugs do not

have the same functional effect in humans when delivered to humans bearing tumors. Moreover, while Applicant discloses malvidin as an inhibitor of colon cells, Katsube et al. (Katsube, N. et al. Journal of Agricultural and Food Chemistry (1/1/2003), 51(1): 68-75. Induction of apoptosis in cancer cells by bilberry (Vaccinium myrtillus) and the anthocyanins.) teaches, "Only pure delphindin and the glycoside isolated from the bilberry extract, but not malvidin and the glycoside, inhibited the growth of HCT 116 cells".

Amount of Experimentation Necessary. The quantity of experimentation necessary to carry out the claimed invention is high, as the skilled artisan could not relay on the prior art or instant specification to teach how to make and/or use the instantly claimed method for *in vivo* suppression in a mammal of multiplicity in the stomach, colon and both the stomach and the colon of cancer cells which comprises providing an effective amount of a composition which consists essentially of malvidin as an active ingredient to the mammal so as to suppress multiplicity of the cells. There is no guidance in the specification, other than the aforementioned examples directed to an *in vitro* method for inhibiting the proliferation of human cell lines of stomach and colon cancer comprising contacting the cells with a dose amount of a composition consisting essentially of malvidin. Given the insufficient guidance in the specification as to how to carry out the instantly claimed invention, the lack of working examples, the lack of correlative working examples, and the state of the art at the time the specification was filed, the claimed method for the *in vivo* suppression of multiplicity of either or both of any and all stomach and any and all colon cancer cells in a mammal comprising the

administration of an effective amount of the claim-designated composition would require an undue amount of experimentation without a predictable degree of success on the part of the skilled artisan.

In response to the rejection made under 35 U.S.C. 112, first paragraph, in the previous Office action, Applicant argues that the instantly claimed invention is enabled and points to specific paragraphs in the specification to support his position. Applicant further points the Examiner to Examples 1 to 5 show treatment of Min mouse with cyanidin is effective in suppressing multiplicity of (cancerous cells) in APC Min mouse, and directs the Examiner to the Declaration under 37 C.F.R. § 1.132 filed by Muraleedharan G. Nair, which also shows that cyanidin is effective in suppressing multiplicity in APC min mouse by reference to the teachings of Kang et al. (Cancer Letters (2003), 194: 13-19. Kang, Soo-Young et al. *Tart cherry anthocyanins inhibit tumor development in Apc^{Min} mice and reduce proliferation of human colon cancer cells.*). Thereby, Applicant concludes, "One skilled in the art would have no basis for saying that the claimed method was not effective in view of the *in vivo* and *in vitro* data." Applicant's arguments, as well as the declaration of Nair have been fully considered but not found persuasive for all of the reasons set forth in the previous Office action and for all of the reasons set forth herein. However, Applicant cannot rely on the teachings of a reference published after the filing of the originally filed specification to provide support for the instantly claimed invention. Furthermore, it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell

interactions. Clearly, an anti-tumor agent must accomplish several tasks to be effective. It must be delivered into the circulation that supplies the tumor and interact at the proper site of action and must do so at a sufficient concentration and for a sufficient period of time. In addition, the target cell must not have an alternate means of survival despite action at the proper site for the drug. *In vitro* assays cannot duplicate the complex conditions of *in vivo* therapy. In the assays, the anti-tumor agent is in contact with cells during the entire exposure period. This is not the case *in vivo*, where exposure at the target site may be delayed or inadequate. In addition variables such as biological stability, half-life or clearance from the blood are important parameters in achieving successful therapy. The specification provides insufficient guidance with regard to theses issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict the efficacy of the claimed method with a reasonable expectation of success based on the similarity of chemical structure between cyanidin and malvidin.

With regard to the Declaration under 37 C.F.R. § 1.132 filed by Muraleedharan G. Nair, full consideration was given to each statement and the teachings of the cited references referred to therein. Nair argues that there is a direct correlation between *in vitro* and oral *in vivo* use in suppressing multiplicity of human cancer cells of the stomach or colon with anthocyanins and cyanidin. Nair also argues that since malvidin is a related compound to cyanidin it would be expected by one skilled in the at that there would be a similar correlation with *in vitro* and *in vivo* use of malvidin to suppress multiplicity of stomach or colon cells. Similarly, Nair relies on the teachings of Kang et

al. to provide support for the instantly claimed invention. Again, Applicant is reminded that Applicant cannot rely on the teachings of a reference published after the filing of the originally filed specification to provide support for the instantly claimed invention. Nonetheless, even in view of the Kang' reference, nowhere does Kang either teach or suggest administering to a mammal in need thereof an effective amount of a composition consisting essentially of malvidin to provide for a method of *in vivo* suppression in a mammal or multiplicity in the stomach, colon and in both the stomach and colon of cancer cells. In fact, Kang neither teaches nor suggests administering either malvidin or administering a cherry diet containing malvidin or consisting essentially of malvidin to the test model (Apc^{Min} mice) to provide an *in vivo* method for the suppression of multiplicity of cancer cells in the stomach or colon of a mammal.

The instant invention, as claimed, falls under the "germ of an idea" concept defined by the CAFC. The court has stated that "patent protection is granted in return for an enabling disclosure, not for vague intimations of general ideas that may or may be workable". The court continues to say that "tossing out the mere germ of an idea does not constitute an enabling disclosure" and that "the specification, not knowledge in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement". (See *Genentech inc v. Novo Nordisk A/S* 42 USPQ2d 1001, at 1005). The claimed methods of transfer constitute such a "germ of an idea".

Given the foregoing, it would take undue experimentation without a reasonable expectation of success for one skill in the art to provide the claimed method for *in vivo* suppression in a mammal of multiplicity in the stomach, colon and in both the stomach

and colon of any and all stomach and/or any and all stomach cancer cells or the claim-designated AGS stomach cancer cell line or the claim-designated HCT 116 colon cancer cell line comprising providing the mammal with an effective amount of a composition consisting essentially of malvidin to suppress multiplicity of the cancerous cells, as broadly claimed by Applicant.

Claim Objections

Claim 7 remains objected to because of the following informalities: There is an apparent typographical error in line 2. Applicant may overcome the objection by replacing "HCT 156" with HCT 116. Appropriate correction is required.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michele Flood whose telephone number is 571-272-0964. The examiner can normally be reached on 7:00 am - 3:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Terry McKelvey can be reached on 571-272-0775. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Michele C. Flood.

MICHELE FLOOD
PRIMARY EXAMINER

Michele Flood
Primary Examiner
Art Unit 1655

MCF
December 15, 2006